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(54) **TREATING MUCOSAL LESIONS WITH HYALURONAN DELIVERED FROM AN ADHERING TROCHE**

BEHANDLUNG VON SCHLEIMHAUTLÄSIONEN MIT AUS EINER BEFESTIGTEN PASTILLE  
BEREITGESTELLTER HYALURONSÄURE

TRAITEMENT DE LÉSIONS DES MUQUEUSES AU MOYEN D'HYALURONANE DÉLIVRÉ PAR UN  
TROCHISQUE ADHÉRENT

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**WO-A1-2013/123487 WO-A2-02/09637**  
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## Description

### FIELD OF THE INVENTION

**[0001]** The present invention relates to methods of topically treating mucosal lesions with hyaluronan released from a slowly dissolving adhering troche, including oral wounds as well as inflammatory, ulcerative and painful conditions such as mucositis, stomatitis, vestibulitis, aphthous ulcerations, lichen planus, and Behcet's syndrome.

### BACKGROUND OF THE INVENTION

**[0002]** Mucositis is an inflammation of mucous membranes. It typically manifests as an erythematous, burn-like lesion or as random, focal-to-diffuse, ulcerative lesions. Stomatitis is an inflammation of mucous membranes in the mouth. About 20 percent of people suffer from recurrent stomatitis in the form of mouth ulcers, mouth sores, canker sores (aphthous ulcers), denture sores, and sores from cuts or braces.

**[0003]** Stomatitis can occur with or without ulceration, and may be caused or intensified by pharmacological, particularly chemotherapeutic treatments, or by radiotherapy. Stomatitis can range from mild to severe; the patient with severe stomatitis is unable to take anything by mouth, contributing to dehydration and malnutrition.

**[0004]** Many women get oral aphthous ulceration at specific times of the menstrual cycle and some simultaneously get similar ulcers in the genital tract, in particular the vulva and vagina. This is sometimes very severe and can cause retention of urine and require strong painkillers and sedatives. The most severe form is called Behcet's syndrome.

**[0005]** Cancer treatment may have toxic effects on normal cells as well as cancer cells. The gastrointestinal tract, including the mouth, is especially affected because cells in the GI tract are replaced continuously by the body. Mucositis in the mouth (e.g., stomatitis), is one of the most common oral problems occurring after chemotherapy and radiation therapy. Oral mucositis can contribute to oral infections, inability to taste normally, and pain arising from the resulting open sores that can develop.

**[0006]** Oral mucositis frequently also occurs in HIV patients, particularly when associated with Kaposi's sarcoma, in patients affected with non-Hodgkin's lymphoma, in debilitated elderly patients and in patients receiving BRM treatments like interleukin-2, TNF, interferons, lymphokine-activated lymphocytes and the like.

**[0007]** WO 2011/006263 and D3 WO 02/09637 disclose compositions comprising hyaluronan for use in the treatment of mucositis.

### SUMMARY OF THE INVENTION

**[0008]** The scope of the invention is defined by the claims. Any references in the description to methods of treatment refer to the products of the present invention

for use in a method for treatment. In one aspect, the disclosure provides a bilayer troche for use in the treatment or prevention of mucositis as defined in claim 1. In certain embodiments, the amount of hyaluronan is at least 10 mg or at least 3% hyaluronan. In some embodiments, the hyaluronan has an average molecular weight of at least 1,500,000 daltons.

**[0009]** The troche may be made in a variety of shapes and sizes. The troche is bilayer, having an adherent layer and a non-adherent layer.

**[0010]** The troche may be used to treat mucositis, including stomatitis or aphthous ulcers, or wherein the mucositis occurs in an oro-pharynx or an oesophagus.

**[0011]** The present invention can be more fully explained by reference to the following detailed description and illustrative examples.

### DRAWINGS

#### **[0012]**

Figure 1 shows a cross section of an adhering troche in a simple shape.

Figure 2 shows a cross section of an adhering troche in a shape designed to adhere well to gums, a tooth, or an orthodontic brace.

Figure 3 shows a cross section of a troche in the form of a patch designed to adhere to mucosal tissue, such as gums, the cheek or lip, vagina, or rectum.

### DETAILED DESCRIPTION

**[0013]** utilizes an adhering troche comprising hyaluronan applied topically close by or in an area exhibiting mucositis. The adherent troche can adhere to gums (keratinized mucosa) or teeth or orthodontic braces as well as to mucosal tissue. Adhering troches for use in the mouth are often called oral adhering discs.

**[0014]** An adhering troche comprises hyaluronan (also called hyaluronic acid or hyaluornate, including sodium hyaluronate), which is an anionic, nonsulfated glycosaminoglycan. The amount of hyaluronan in a troche should be an effective level, a level sufficient to treat mucositis. The troche comprises at least 5 mg of hyaluronan, or at least 7 mg, or at least 10 mg. In certain embodiments, hyaluronan is at least 2% w/w of the troche ingredients, or at least 3%, or at least 5%, or at least 10%, or at least 20%. The troche has a bilayer structure and when an adhesive other than hyaluronan is used in the adhering layer, the percentage of hyaluronan is at least 2%, or at least 3%, or at least 5%, or at least 10%, or at least 20% of the non-adherent layer.

**[0015]** Hyaluronan comprises disaccharides of D-glucuronic acid and D-N-acetylglucosamine. In vivo, polymers of hyaluronan can range in size from about 5,000 to about 20,000,000 Da. Generally, a higher average molecular weight is used, but may have with a trade-off of cost and uniformity. In some embodiments, hyaluronan

has a molecular weight of at least 500,000 Da, or at least  $1 \times 10^6$  Da, or at least  $1.5 \times 10^6$  Da, or at least  $5 \times 10^6$  Da, or at least  $10 \times 10^6$  Da. The hyaluronan may be extracted from natural sources such as chickens or bacteria that make hyaluronan. Hyaluronan is available commercially from both of these sources.

**[0016]** An adhering troche may comprise other ingredients, including, for example, one or more adhesives (e.g., acacia gum), one or more binders (e.g., cellulose gum, acacia gum), one or more flavorings (e.g., licorice), one or more medicaments, one or more vitamins, one or more excipients (e.g., salts, buffers), one or more viscous and lubricating substances (e.g., cellulose gum), and one or more adjuvants. In some embodiments only one additional ingredient may be present, in other embodiments, multiple other ingredients may be present. Compositions of other ingredients are well-known in the art.

**[0017]** The troche can adhere to gums or teeth, structures attached to teeth (e.g., orthodontic braces), or oral mucosal tissue. Hyaluronan itself is muco-adhesive and may comprise all or nearly all of the ingredients of an adhesive troche.

**[0018]** The adhering troche will generally release hyaluronan over a long dissolution time, such as 1-8 hours, for topical application to nearby tissues. Typically, the adhering troche that contains hyaluronan completely dissolves. More precisely, hyaluronan and the binder molecules and other ingredients slowly erode. Some suitable binder molecules are acacia gum and cellulose gum. Optionally, the troche may be made with slowly dissolving hydrocolloids so that that it typically lasts in the mouth for at least ten minutes and up to about six hours. A benefit of delivering hyaluronan with an adhering troche rather than a non-adhering troche (lozenge) is that this allows the troche to be used safely in the mouth while sleeping when saliva flow is lowest and the hyaluronan will linger longest in the mouth. Such a troche may be designed to last 6-8 hours while sleeping.

**[0019]** To ensure that the troche dissolves (erodes) slowly in saliva, a binder that dissolves slowly in saliva is incorporated. Some suitable binders include carrageenan (especially kappa form), xanthan gum, xanthan gum combined with konjac gum, agar, and cellulose gums such as carboxymethylcellulose (CMC), hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC). Other gums similar to those listed, such as locust bean gum which has properties similar to konjac gum, and guar gum are also suitable, as well as starches, such as corn starch or, particularly pregelatinized corn starch.

**[0020]** In one embodiment, a troche comprises hyaluronan, collagen and other binder ingredients. Collagen, which is the organic molecule that makes up skin and the lining of the mouth (a form of skin), tends to adhere very well to itself, making it glutinous, and therefore adheres very well to mucous tissues. An effective and cost effective form of collagen is food grade gelatin, which is made from animal skins.

**[0021]** The troche may be formed in a variety of shapes and sizes. A side view of a few exemplary shapes are illustrated in Figures 1-3. Fig. 1 shows a troche in the shape of a tablet or lozenge. Fig. 2 shows an exemplary troche that is "dimpled" on one side. Fig. 3 shows a troche in the shape of a thin lentil, often called a patch. This troche is nearly or essentially flat on one side. Many other shapes can be used. When viewed from the top or bottom, troches may be a variety of shapes, and usually will be round or oval. Choice of shape will be based on a number of factors, including ease and cost of manufacturing, surface intended for the troche to adhere, or consumer preference.

**[0022]** The size of a troche will generally also take into account the ease and cost of manufacturing, surface intended for the troche to adhere, or consumer preference. In general, a troche will range from about 5-20 mm or from about 5-18 mm, or from about 7-18 mm, or from about 10-15 mm in at least two dimensions. When the troche is round or nearly round, the size range represents suitable diameters. The thickness of a troche will generally be from 1-10 mm, and more generally from 3-5 mm.

**[0023]** Many suitable manufacturing methods may be used and are well known in the art. One exemplary method of manufacturing troches in the shape of patches is to use gum drop manufacturing equipment, squirting a hydrated mixture heated above the gel melting temperature through nozzles onto a sheet of plastic or coated paper, allowing the troches to cool and gel, and drying the troches. The troches are typically dried until the water activity level is lower than 0.8 to reduce growth of mold or other organisms. The drops are allowed to cool and then the sheets of plastic or coated paper with the drops on them are dried in a drying chamber. The product can be sold still adhered to the plastic or paper, and the user pulls it off the plastic or paper. Other methods for making adherent troches include extrusion of a sheet and then die cutting.

**[0024]** Troches in the form of bi-layer dissolving mucoadhesive tablets for use in the mouth may be made by pressing powders including mucoadhesive hydrocolloids. An exemplary, bilayer adhering troche may be made by mixing dry powders comprising at least 80 percent acacia gum (gum arabic) in the adhesive layer, and may comprise at least 90 percent. The non-adhesive layer may include 20-70% acacia gum as a binder, 5-40% cellulose gum as a binder and moist tissue coating agent, and 2 - 50% hyaluronan. The tablet may be pressed into two layers which, combined, make the shape shown in Figure 2, which adheres well to a tooth or gums or orthodontic brace. Such a tablet is usually 9-14 mm in diameter and 120-500 milligrams in weight. It lasts 1-8 hours in the mouth, most commonly 2-4 hours.

**[0025]** A method for treating or preventing mucositis inflammation in a patient comprises administering to a patient in need thereof an effective number of adhering troches each comprising at least 5 mg of hyaluronan. An effective level of use of the adhering troche comprises

enough hyaluronan to deliver a dose to mucosa equal to at least 5 mg of hyaluronan spread over nearby tissues in a mouth, or at least 10 mg. Optimally, the dissolution time for such a troche is 1 to 8 hours. Because the troches adhere, they will remain in desired locations to treat immediately nearby areas with continuous high concentrations of hyaluronan delivered over time.

**[0026]** The adhering troche may be administered at least once daily every day without end to prevent or reduce the effects of mucositis. In addition to its ordinary meaning, the term treatment encompasses inhibition of progression of symptoms or amelioration of symptoms of inflammation and mucositis. These methods may provide an effective therapeutic or preventive treatment for mucositis and stomatitis of various origins and severity and, more generally, of the lesions of the oro-pharynx cavity and oesophagus, particularly those caused by recurrent aphthous ulceration, dental devices, by radio- or chemotherapy, and by surgery. The troches may be used to treat oral wounds as well as inflammatory, ulcerative and painful conditions such as mucositis, stomatitis, vestibulitis, aphthous ulcerations, lichen planus, and Behcet's syndrome.

**[0027]** Without being bound by a particular mode of action or theory, favorable therapeutic results obtained by the use of the adhering troches comprising hyaluronan are believed to be due to interactions between molecules of hyaluronan with elements of the healing process or the ulceration process.

**[0028]** A typical instruction to users for oral mucositis is to adhere a troche in their mouths, especially near the site of mucositis, as needed. The troches may be supplied in a kit, comprising one or more adherent troche and instructions for use. Troches may be applied continuously, one after another, both during the day and just before sleep, adhering the troche to teeth or gums near the sore so that the hyaluronan as it is released from the troche will coat the sore. Tenderness may inhibit users from applying a troche to the sore.

**[0029]** In a particular embodiment in which the adhering troche is administered to the oral cavity, the patient, after applying a dissolving troche, if desired, may refrain from eating or drinking for a certain time, ranging from minutes up to hours.

**[0030]** Such troches were given to test subjects with the above instructions, generating good results in pain reduction while a troche was dissolving and good speeding of healing of aphthous ulcers triggered by bites.

**[0031]** The following examples are presented by way of illustration and not by way of limitation on the scope of the invention.

## EXAMPLES

### EXAMPLE 1

**[0032]** A bi-layer troche comprising hyaluronan is manufactured. The adhesive layer comprises at least 80 per-

cent acacia gum (gum arabic) as an adhesive, and may comprise at least 90 percent. The non-adhesive layer includes 20-70% acacia gum as a binder, 5-40% cellulose gum as a binder and moist tissue coating agent, and magnesium stearate as a manufacturing lubricant. The tablet comprises 2-5% hyaluronan. The tablet is pressed into two layers which, combined, make the shape shown in Figure 2 for good adhesion to a tooth or gums or orthodontic brace. The tablet is 12 mm in diameter and weighs about 100 milligrams in the adhesive layer and 250 milligrams in the non-adhesive layer.

## Claims

1. A bilayer troche for use in the treatment or prevention of mucositis, having an adherent layer and a non-adherent layer, wherein the treatment or prevention of mucositis comprises applying the adhering troche to a mucosal surface or a tooth or orthodontic brace of a patient in need thereof, and wherein the adhering troche is applied just before sleeping, comprising at least 5 mg hyaluronan, and wherein hyaluronan is released from the troche.
2. The troche for use as in claim 1, wherein the troche comprises at least 10 mg hyaluronan.
3. The troche for use as in claim 1, wherein the non-adherent layer comprises at least 2% and up to 50% hyaluronan, at least 20% and up to 70% acacia gum as a binder, and/or at least 5% and up to 40% cellulose gum as a binder and moist tissue coating agent.
4. The troche for use as in any of claims 1-3, wherein the hyaluronan has an average molecular weight of at least 500,000 daltons.
5. The troche for use as in any of claims 1-3, wherein the hyaluronan has an average molecular weight of at least 1,500,000 daltons.
6. The troche for use as in any of the preceding claims for the use in preventing mucositis, wherein the adhering troche is applied at least once a day every day.
7. The troche for use as in any of the preceding claims, wherein the mucositis is stomatitis or aphthous ulcers.

## Patentansprüche

1. Zweilagige Tablette zur Verwendung bei der Behandlung oder Prävention von Mukositis, die eine haftende Lage und eine nichthaftende Lage aufweist, wobei die Behandlung oder Prävention von

- Mukositis umfasst, die haftende Tablette auf eine Schleimhautoberfläche oder einen Zahn oder eine kieferorthopädische Zahnsperre eines Patienten, der dessen Bedarf, aufzubringen, und wobei die haftende Tablette kurz vor dem Schlafengehen aufgebracht wird, enthaltend mindestens 5 mg Hyaluronan, und wobei Hyaluronan aus der Tablette freigesetzt wird. 5
2. Tablette zur Verwendung gemäß Anspruch 1, wobei die Tablette mindestens 10 mg Hyaluronan enthält. 10
3. Tablette zur Verwendung gemäß Anspruch 1, wobei die nichthaftende Lage mindestens 2% und bis zu 50% Hyaluronan, mindestens 20% und bis zu 70% Akaziengummi als Bindemittel und/oder mindestens 5% und bis zu 40% Cellulosegummi als Bindemittel und Feuchtgewebebeschichtungsmittel enthält. 15
4. Tablette zur Verwendung gemäß einem der Ansprüche 1 - 3, wobei das Hyaluronan ein durchschnittliches Molekulargewicht von mindestens 500.000 Dalton hat. 20
5. Tablette zur Verwendung gemäß einem der Ansprüche 1 - 3, wobei das Hyaluronan ein durchschnittliches Molekulargewicht von mindestens 1.500.000 Dalton hat. 25
6. Tablette zur Verwendung gemäß einem der vorstehenden Ansprüche zur Verwendung bei der Prävention von Mukositis, wobei die haftende Tablette mindestens einmal täglich aufgebracht wird. 30
7. Tablette zur Verwendung gemäß einem der vorstehenden Ansprüche, wobei die Mukositis Stomatitis oder aphthöse Ulzera sind. 35

## Revendications

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1. Pastille bicouche destinée à l'utilisation dans le traitement ou la prévention de la mucosite, possédant une couche adhérente et une couche non-adhérente, dans laquelle le traitement de prévention de la mucosité comprend l'application de la pastille adhérente sur une surface muqueuse ou une dent, ou un appareil orthodontique d'un patient en ayant besoin, et dans laquelle la pastille adhérente est appliquée juste avant le sommeil, comprenant au moins 5 mg de hyaluronane et dans laquelle le hyaluronane est relâché de la pastille. 45 50
2. Pastille destinée à l'utilisation telle que dans la revendication 1, dans laquelle la pastille comprend au moins 10 mg d'hyaluronane. 55
3. Pastille destinée à l'utilisation telle que dans la re-

vendication 1, dans laquelle la couche non adhérente comprend au moins 2% et jusqu'à 50% d'hyaluronane, au moins 20% et jusqu'à 70% de gomme d'acacia en tant que liant, et/ou au moins 5% et jusqu'à 40% de gomme cellulose en tant que liant et un agent de revêtement de tissu humide dans la couche non adhérente.

4. Pastille destinée à l'utilisation telle que dans une quelconque des revendications 1 à 3, dans laquelle l'hyaluronane possède un poids moléculaire moyen d'au moins 500.000 daltons.

5. Pastille destinée à l'utilisation telle que dans une quelconque des revendications 1 à 3, dans laquelle l'hyaluronane possède un poids moléculaire moyen d'au moins 1.500.000 daltons.

6. Pastille destinée à l'utilisation telle que dans une quelconque des revendications précédentes en vue de l'utilisation dans la prévention de la mucosite, dans laquelle la pastille adhérente est appliqué chaque jour au moins une fois par jour.

7. Pastille destinée à l'utilisation telle que dans une quelconque des revendications précédentes, dans laquelle la mucosite est une stomatite ou des ulcères aphteux.

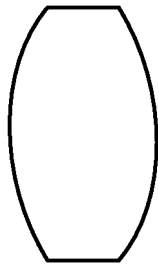


Figure 1



Figure 2



Figure 3

**REFERENCES CITED IN THE DESCRIPTION**

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